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Editorial Comment

Creatine Kinase Release After Brief Coronary Occlusion*

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The clinical application of cardiac enzymology is based on the generally held opinion that increased levels of myocardial enzymes in the peripheral blood indicate that myocardial cell death has occurred. The implications of this notion are that 1) certain enzymes are present only in the myocardium, and 2) they are not released with reversible forms of myocardial injury. Both of these concepts have been challenged in clinical and experimental studies.

Creatine kinase-MB (CK-MB) has been demonstrated in organs other than the heart (1); small amounts are present in the gastrointestinal tract, urinary system, liver, central nervous system and, rarely, in neoplasms (2). In patients with cardiomyopathy and in marathon runners, substantial amounts of CK-MB have been demonstrated in skeletal muscle (3). In acute ischemic syndromes, these sources of enzyme usually do not limit the utility of serum measurements of CK-MB. However, if CK-MB is released from ischemic but noninfarcted myocardium, extensive reevaluation of current diagnostic and therapeutic strategies would be necessary. Most experimental studies in intact animals, isolated hearts and individual cells in culture, using a number of models of ischemia and a variety of techniques for detecting necrosis, have shown that cell death (necrosis or irreversible injury) is required for detectable enzyme leakage from myocardial cells. Other studies in comparable systems and using similar techniques, however, have been reported to demonstrate enzyme leakage from myocardial cells in the absence of cell death. Thus, it was concluded from these latter studies that reversible myocardial injury that does not cause cell death can result in alterations of cell membrane permeability with release of myocardial enzymes.

The study by Heyndrickx et al. (4) in this issue of the Journal provides additional data supporting the minority opinion. The authors found that in six instrumented baboons with 15 minutes of closed chest left anterior descending coronary artery occlusion followed by 24 hours of reflow there was substantial release of CK and CK-MB into the peripheral blood in the absence of myocardial necrosis at autopsy. They concluded that the CK must have been released from the ischemic, but not the necrotic, myocardium.

Methodologic considerations. How does one (like me) whose preconceived bias and observations (5,6) suggest that necrosis is necessary for CK release attempt to discount the findings of Heyndrickx et al.? It is difficult. In the first place, it is unlikely that the substances being measured in the blood were not CK and CK-MB. Second, in a reperfusion model, with animals killed 24 hours after coronary occlusion, it is not difficult to detect myocardial necrosis, especially because gross histochemical staining (triphenyltetrazolium chloride [TTC]) and histologic examination were both employed. Third, a noncardiac source of the elevated CK blood levels seems very unlikely because no such elevation was observed in control, instrumented animals that had no coronary occlusion.

The staunch skeptic, however, might have preferred more methodologic details assuring exhaustive sampling of each heart, with special emphasis on possible "artifactual" sources of CK release, such as the myocardium adjacent to the occluded artery, which could have been traumatized by the hydraulic occluder or the artery itself which could have been the source of CK. In our laboratory, we have observed that vigorous clamping of a peripheral artery results in elevation of total CK in the blood distal to the site of mechanical trauma (unpublished observations). Furthermore, the authors' findings would have been more conclusive if they had shown decreased CK levels in the ischemic myocardium. Because CK levels were measured in the normal myocardium and the ischemic zones were identifiable by the microsphere studies, these data could have been obtained. An additional control to exclude CK release related to the trauma of coronary occlusion, such as a few seconds of coronary occlusion followed by reflow, would also have been desirable.

Are there any other aspects of this study that merit additional consideration before its conclusions are accepted? Why in this reperfusion model was the time to peak CK release unusually long (9.3 hours) (7)? Why was there metachronous peaking of total CK (9.3 hours) and CK-MB (4.5 hours), which is not typical in clinical myocardial infarction (8)? If, as the authors suggest, the findings can be explained by gradual, prolonged membrane damage leading to increased permeability, then why wouldn't other enzymes leak out, such as the diaphorases, dehydrogenases and reduced coenzymes that are responsible for normal TTC staining of myocardium (9)?

Clinical implications. Admittedly, many of these comments might seem insignificant, were this not a subject of such clinical importance. In patients with acute ischemic syndromes, can elevated blood levels of CK and CK-MB

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no longer be regarded as diagnostic of myocardial infarction? Did patients who had percutaneous transluminal coronary angioplasty and subsequently demonstrated elevated blood CK levels have myocardial necrosis, transient myocardial ischemia or simply coronary artery trauma? Can CK peaks and curves be used to estimate infarct size if CK release occurs in the absence of necrosis?

To prove that ischemia can result in elevated levels of CK-MB in the peripheral blood, the source of the CK-MB must be identified as the ischemic myocardium. All other sources such as traumatized myocardium or coronary artery must be excluded. The findings of Heyndrickx et al. remind us of several well known facts: 1) There is no perfect laboratory test; 2) biologic systems are rarely as straightforward as we would like to believe; and 3) more studies are always needed.

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